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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/804,214	03/19/2004	Arthur M. Brown	T2074-00039	6520

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EXAMINER	
GABEL, GAILENE	
ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/804,214	BROWN ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,7-9,19,20 and 30-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7-9,19,20 and 30-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response, filed on August 27, 2007, is acknowledged and has been entered. Claims 1, 2, 7, 9, 19, 20, 30, and 31 have been amended. Claims 4, 6, 10-18, and 21-29 have been cancelled. Accordingly, claims 1-3, 5, 7-9, 19, 20, and 30-35 are pending and are under examination.

Specification

2. The disclosure is objected to because of the following informalities: In the specification at page 16, last full paragraph, an ampersand appears after "(Aa capture antibody@)" in two occurrences. Please correct or clarify. This objection is being maintained.

Appropriate correction is required.

Withdrawn Rejections or Objections

3. All objections or rejections not reiterated herein, have been withdrawn.

4. The rejections of claims 4 and 6 are now moot in light of Applicant's cancellation of the claims.

5. In light of Applicant's amendment, the rejection of claims 1-3, 5, 19 and 20 under 35 U.S.C. 102(b) as being anticipated by Woska et al. (US 2002/0068305 A1) in light of

Isacke (Integrin α_I, The Adhesion Molecule FactsBook, second edition (2000) 149-151), is hereby, withdrawn.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-3, 5, 7-9, 19, 20, and 30-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, step e) in line 3 lacks antecedent basis for the recitation of "said protein", first and second occurrence.

Claim 1, step f) in line 5 lacks antecedent basis for the recitation of "said protein".

Claim 1, step f) lacks antecedent basis for the recitation of "said at least one antibody in an amount equal to that in step d)", since there does not appear to be an antibody recited in step d).

Claim 30 is objected to for depending from a cancelled claim.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-3, 5, 7-9, 19, 20, and 30 are rejected on the ground of nonstatutory double patenting over claims 1-24 of US Patent 7,211,407 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent. This rejection is being maintained for reasons of record.

8. Claims 1-3, 5, 7-9, 19, 20; and 30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-24 of US Patent 7,211,407 in view of Zhang et al. (The Extracellular Domain Suppresses Constitutive Activity of the Transmembrane Domain of the Human TSH Receptor: Implications for Hormone-Receptor Interaction and Antagonist Design, Endocrinology 141 (9): 3514-3517 (2000)). This rejection is being maintained for reasons of record.

It is noted that Applicant will submit the appropriate terminal disclaimer when the allowable subject matter is indicated in this application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-3, 5, 7-9, 19, 20, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woska et al. (US 2002/0068305 A1) in view of Curtis (US 2003/0022205) and in further view of Zhang et al. (Endocrinology 141 (9): 3514-3517 (2000)).

Woska et al. provide a method of identifying an agent (chemical compound) that alters (modifies) the level of surface expression of CD11a subunit of LFA-1 protein [0002]. In practice, a medium containing mammalian cells (peripheral blood mononuclear cells) is combined with the agent and then the mixture is incubated for a period of time. Thereafter, the cell mixture is contacted with a labeled antibody that specifically binds the R7.1 (extracellular) epitope of LFA-1 whereupon a fluorescent

signal is produced by the binding of the antibody to the R7.1 epitope. In another embodiment, a primary antibody that specifically binds the R7.1 epitope and a secondary labeled antibody the binds the primary antibody may be used whereupon a fluorescent signal is produced by the binding of the antibody to the R7.1 epitope. In either case, the level (increase or decrease) of binding of the R7.1 antibody to the R7.1 epitope of LFA-1 indicates alteration of the surface expression of LFA-1 protein [0011-0014], [0017], [0019], [0021-0023] and [0029]. Woska et al. exemplify treating the cells with a fixative [0639]. Woska et al. disclose application of the method in different assay formats wherein the level of binding is measured by immunofluorescence, radioactivity (radioisotopes), and absorbance [0613], [0616], and [0617]. Enzyme labels that can be used with the method include alkaline phosphatase and horseradish peroxidase [0615]. In as far as the recitation of "at least one extracellular epitope comprises a wild-type epitope" in claim 5, absent any teaching in the Woska reference of the use of cells in mutant form, it is presumed that the LFA-1 molecules in the cells used by Woska are wild-type.

Woska et al. differ from the instant invention in failing to teach that the protein is a membrane ion channel.

Curtis teaches screening of compounds which modulate expression of the cell surface protein 98359 (see [0242], [0243], and [0272]). Protein 98359 is an integral, transmembrane cell surface molecule involved in sodium transport; hence, involved in membrane ion channel (see [0036]). The level of 98359 protein expression can be determined using antibodies by direct or indirect labeling (see [0319]). Curtis

specifically provides that the antibodies can be directed to extracellular portion of the protein 98359; thus, bind to extracellular epitope on an intact cell which expresses this protein (see [0201]).

Woska et al. and Curtis differ from the instant invention in failing to teach that the extracellular epitope contains a tag which replaces at least a portion of an extracellular domain of the protein.

Zhang et al. provide that TSH receptors (TSHR) are very susceptible to constitutive activation by mutations in various regions of the molecule, including mutations in the extracellular domain (ECD) and extracellular loops of the transmembrane domain. To understand the role of ECD in TSHR, Zhang et al. test several TSHR constructs having major deletions (mutations) of the ECD. Specifically, Zhang et al. perform studies on ligand-binding and basal constitutive activation using TSHR tagged at its N-terminus with a hemagglutinin tag, i.e. inserted, recognized by HA-specific monoclonal antibody (see Abstract). The cells are cultured, fixed with paraformaldehyde, and then quantified for expression of HA epitope-tagged TSHR constructs using HA specific monoclonal antibody. Zhang et al. teach using enzyme label (peroxidase) for the method, whereupon enzymatic reaction is measured by Absorbance at 450 nm. (see page 3515, column 1).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to insert an HA tag recognized by HA specific monoclonal antibody as taught by Zhang into the extracellular domain of the 98359 protein taught in the method of Woska as modified by Curtis because Zhang specifically taught that insertion of HA

tag into extracellular domain of the proteins provides reliable assessment of ligand-binding and basal constitutive activities, leading to a better understanding of the role of extracellular domains for cell surface expression of membrane ion channel.

10. Claims 1-3, 5, 7-9, 19, 20, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woska et al. (US 2002/0068305 A1) in view of Vallone (US 2004/0018566) and in further view of Zhang et al. (Endocrinology 141 (9): 3514-3517 (2000)).

Woska et al. is discussed supra. Woska et al. differ from the instant invention in failing to teach that the protein is a membrane ion channel.

Vallone et al. teach screening for compounds which modulate expression of the cell surface protein BIC (see [0316-0319]. The BIC protein 98359 is an integral, transmembrane cell surface molecule involved in cation transport; hence, involved in membrane ion channel (see [0021]-[0024]). The level of BIC protein expression can be determined using antibodies by direct or indirect labeling that are directed against extracellular epitope of the BIC protein expressed in intact cells (see [0382]).

Woska et al. and Vallone et al. differ from the instant invention in failing to teach that the extracellular epitope contains a tag which replaces at least a portion of an extracellular domain of the protein.

Zhang et al. is discussed supra.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to insert an HA tag recognized by HA specific monoclonal antibody as

taught by Zhang into the extracellular domain of the BIC protein taught in the method of Woska as modified by Vallone because Zhang specifically taught that insertion of HA tag into extracellular domain of the proteins provides reliable assessment of ligand-binding and basal constitutive activities, leading to a better understanding of the role of extracellular domains for cell surface expression of membrane ion channel.

10. Claims 31-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woska et al. (US 2002/0068305 A1) in view of Curtis (2003/0022205) or Vallone (2004/0018566) and in further view of Zhang et al. (Endocrinology 141 (9): 3514-3517 (2000)), as applied to claims 1-3, 5, 7-9, 19, 20, and 30 above, and further in view of Owman et al. (US 2002/0150912 A1).

Woska et al., Curtis or Vallone et al., and Zhang et al. are discussed supra. Woska et al., Curtis or Vallone et al., and Zhang et al. differ from the instant invention in failing to teach that the membrane ion channel contains a fluorescent tag which replaces at least a portion of an intracellular domain of the protein.

Owman et al. provide chimeric reporter constructs, recombinant cells containing the reporter constructs, and assays utilizing the recombinant cells for detection of substances that interact with integral membrane proteins such as G-protein coupled receptors (GPCRs) that act through calcium mobilization and signal through the mitogen-activated protein (MAPK) cascade (see Abstract and [0016] [0018] [0048]. In the high-throughput screening assay, recombinant cells expressing the integral membrane protein are combined with a large number of substances. Interaction with a

substance causes the receptor to generate a signal that subsequently activates the reporter gene in the reporter construct, the level of expression of which is monitored using fluorescent or luminescent signal [0072]. The chimeric reporter construct comprises sequences encoding a green fluorescent protein (GFP) inserted at an intracellular domain of the protein [0017] [0056]. According to Owman et al., the reporter construct and recombinant cells are well-suited for high-throughput screening assays of substances that interact with cell surface receptors. Due to intrinsic fluorescence of GFPs, the need to pre-load substrate molecules in order to detect cells that express the reporter gene is not required; hence, cell handling is simple yet robust for a highly sensitive assay system (see Abstract and [0017].

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the fluorescent tag as taught by Owman into the method of identifying agents that alter cell surface expression of membrane ion channel as taught by Woska, modified by Curtis or Vallone, and further modified by Zhang, because Owman specifically taught that in incorporating use of intrinsic fluorescence of GFPs in cell-based assay systems, the need to pre-load substrate molecules in high-throughput screening assays for substances that interact with cell surface receptors, is not required; hence, cell handling is simple yet robust for a highly sensitive assay system.

Response to Arguments

11. Applicant's arguments with respect to claims 1-3, 5, 7-9, 19, 20, and 30-35 have been considered but are moot in view of the new grounds of rejection.

12. No claims are allowed.

13. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 8:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gailene R. Gabel
Primary Examiner
Art Unit 1641

November 6, 2007